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(54) Title: OPHTHALMIC COMPOSITIONS COMPRISING BENZYLLAURYLDIMETHYLAMMONIUM CHLORIDE

(57) Abstract

An ophthalmic solution generally includes an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride and lauralkonium chloride present in an anti-microbially effective amount. The incompatibility of the ophthalmologically acceptable drug manifests itself by forming insoluble ion pairs with the benzalkonium chloride. It has been found that lauralkonium chloride which is the C_{12} homolog of benzalkonium chloride is effective as a preservative without apparent interaction with the acidic ophthalmologically acceptable drug and formulations maintain their antimicrobial efficiency over periods of up to one year or more.

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OPHTHALMIC COMPOSITIONS COMPRISING BENZYLLAURYLDIMETHYLAMMONIUM CHLORIDE

The present invention generally relates to improved ophthalmic formulations and solutions and more particularly to improved preservative systems for ophthalmologically acceptable drug formulations which have an incompatibility with benzalkonium chloride. More specifically, the present invention pertains to the preservative for an anti-inflammatory drug such as sodium flurbiprofen (Ocufen®).

Ophthalmologically acceptable drug formulations generally contain effective compounds and a number of ophthalmologically acceptable excipients. Such excipients generally include solutions, ointments, and suspensions, etc. More specifically, such excipients include stabilizing agents, surfactants, buffering systems, chelating systems, viscosity agents, and, importantly, a preservative.

Ophthalmic formulations, understandably, must be sterile and if a multi-dose regime is intended, the formulation must be preserved with an effective antimicrobial agent.

As discussed in U.S. Patent No. 5,110,493, organo-mercurials have been used extensively as the preservatives in ophthalmic solutions. As reported in this reference, these compounds pose difficulties due to potential mercury toxicity as well as poor chemical stability.

Therefore, benzalkonium chloride, which is a quaternary ammonium compound, has been widely used in ophthalmic solutions. It is also well-known, however, that benzalkonium chloride is considered incompatible with anionic drugs, forming insoluble compounds which cause the solution to turn cloudy.

This is because of the fact that many acidic drug entities carry a negative charge at physiological pH. In fact, all acidic drug entities will carry a negative charge at all pH above their pKa.

In the case of benzalkonium chloride, which is a positively charged preservative, ion pairs can be formed with negatively charged drug compounds, forming an insoluble ion pair which causes the drug to precipitate out of solution. Concomitant with the removal of the drug from solution is the removal of benzalkonium chloride, thereby rendering this quaternary germicide incapable of performing its function as an antimicrobial agent.

Benzalkonium chloride is a mixture of alkyldimethylbenzyl-ammonium chloride of the general formula as shown below in which R represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$

As hereinbefore noted, it is well-known that benzalkonium chloride is generally incompatible with anionic detergents or anionic drug compounds.

See U.S. Patent No. 5,110,493, and The Merck Index, 11th Edition, Merck & Co., Inc., 1989.

The present invention specifically relates to the discovery that a particular member of a group of compounds, generally known as benzalkonium chloride, exhibits properties totally different from other members of the group and different from the gross properties of the mixture known as benzalkonium chloride.

This discovery by the applicant must be taken in the context that all compositions are made of the same substances, retaining their fixed chemical properties. The elements are capable of an infinity of permutations, and selection of that group or element of a group which proves serviceable to a given need requires a high degree of originality. This general premise relates to the invention at hand. The applicant has discovered that lauralkonium chloride, which is the C_{12} homolog of benzalkonium chloride, is compatible with acidic drug entities with apparently no insoluble ion pairs being formed therewith. This is contrary to the properties of the mixture of alkyldimethylbenzylammonium chloride, known as benzalkonium chloride, which includes a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$.

SUMMARY OF THE INVENTION

An ophthalmic solution, in accordance with the present invention, generally includes an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride and lauralkonium chloride present in an antimicrobially effective amount. More specifically, flurbiprofen is an example of an acidic drug that forms an insoluble ion-

pair with benzalkonium chloride. However, when combined with lauralkonium chloride, no apparent insoluble ion pairs are formed.

More particularly, in accordance with the present invention, the ophthalmic solution may further include citric acid monohydrate, sodium citrate dihydrate, polyvinyl alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride and water.

The amount of lauralkonium chloride is any antimicrobially effective amount and preferably may be up to about 0.005% by weight per volume of the solution, and the amount of sodium flurbiprofen may be present in any effective amount and preferably about 0.03% by weight per volume.

The combination of lauralkonium chloride is further emphasized in that it can be combined with an acidic ophthalmologically acceptable drug formulation having a negative charge at physiological pH, and further the fact that the acidic ophthalmologically acceptable drug is capable of forming an insoluble ion-pair with benzalkonium chloride, no apparent insoluable ion-pairs are produced when the drug is in combination with lauralkonium chloride, taken itself.

Further, the invention includes a method for preserving an acidic ophthalmologically acceptable drug solution, comprising adding to the ophthalmologically acceptable drug solution an antimicrobially effective amount of lauralkonium chloride.

DETAILED DESCRIPTION

Flurbiprofen is a classic example of an acidic drug that forms an insoluble ion-pair with benzalkonium chloride. It has been discovered that this interaction (insoluble ion-pair formation) can be overcome by formulating the flurbiprofen with the C_{12} homolog of benzalkonium chloride and lauralkonium chloride.

The lauralkonium chloride utilized will comprise at least 95% and preferably about 97.8% of the C_{12} homolog, 1.5% of the C_{14} homolog, and 0.7% of the C_{16} homolog.

The following examples, illustrating the utility of lauralkonium chloride as opposed to benzalkonium chloride, include the preparation or compounding of flurbiprofen formulations as follows.

Compounding occurs in two parts:

Part 1: Disperse polyvinyl alcohol in rapidly stirring purified water and heat to 85°C. Maintain temperature and stirring for one hour to dissolve the polyvinyl alcohol.

Part 2: While mixing a bulk of purified water of at least 50% of the final lot volume, add edetate disodium, benzalkonium chloride or lauralkonium chloride, potassium chloride, sodium chloride, sodium citrate and citric acid allowing each to dissolve or mix well before adding the next. Adjust the pH to 6.4-6.6 with dilute sodium hydroxide and/or hydrochloric acid. Add sodium flurbiprofen to the bulk and mix well.

While mixing Part 2, add Part 1 and mix thoroughly. Adjust the pH to 6.4-6.6 with dilute sodium hydroxide and/or hydrochloric acid. Sterilize the lot by filtration (0.22μ) and aseptically fill units into pre-sterilized containers.

The benzalkonium chloride and the lauralkonium chloride utilized in the present examples were obtained from E.M. Industries, Inc. of Hawthorne, NY and Triple Crown Ammerica, Inc. of Perkasie, PA, respectively.

Example

Table 1 shows the ingredients for Examples A and B, with the formulations being identical, except that Example A utilizes benzalkonium chloride and Example B utilizes lauralkonium chloride in the same amounts, i.e., 0.005%, by weight per volume.

TABLE 1

OCULEN® FORMULATIONS

Ingredient	Example A	Example B
	% w/v	% w/v
Sodium flurbiprofen	0.03	0.03
Benzalkonium chloride	0.005	-
Lauralkonium chloride	-	.005
Citric acid monohydrate USP	0.05	0.05
Sodium citrate dihydrate USP	0.45	0.45
Polyvinyl alcohol 20-90 Grade	1.4	1.4
Edetate disodium dihydrate USP	0.0127	0.0127

Sodium chloride USP	0.65	0.65
Potassium chloride USP	0.075	0.075
Purified water USP	qs to 100	qs to 100
Sodium hydroxide NF	pH 6.4 to 6.6	pH 6.4 to 6.6
Hydrochloric acid NF	pH 6.4 to 6.6	pH 6.4 to 6.6

Example A results in a cloudy solution with precipitate and loss of antimicrobial efficacy while Example B remains as a solution and the solution maintains its antimicrobial efficacy. Example A failed to pass the preservative effectiveness test as described in the British Pharmacopeia while Example B passes the British Pharmacopieia preservative effectiveness test.

In addition, the ability of lauralkonium chloride to stay in solution and to maintain its antimicrobial effectiveness as a function of time was also monitored. Table 2 shows the concentration of lauralkonium chloride in the formulation described in Example B. Table 3 shows the ability of lauralkonium chloride to maintain its antimicrobial efficacy over a period of up to one year or more.

TABLE 2

No. of Days	Lauralkonium chloride - ppm
13	46.0
32	46.0
75	45.8
115	45.0
192	47.7

370	48.2

TABLE 3

No. of Days	Microbiology Results
13	Pass BP-88
370	Pass BP-88

Although there has been hereinabove described a specific ophthalmic solution and method in accordance with the present invention, for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. An ophthalmic solution comprising:

an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride; and

a preservative consisting essentially of lauralkonium chloride and present in an antimicrobially effective amount.

2. The ophthalmic solution according to Claim 1 wherein said ophthalmologically acceptable drug formulation comprises sodium flurbiprofen.

3. The ophthalmic solution according to claim 2 further comprising citric acid monohydrate, sodium citrate dihydrate, polyvinyl alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride, and water.

4. The ophthalmic solution according to Claims 1, 2 or 3 wherein said lauralkonium chloride is present in an amount up to about 0.005% by weight per volume of the solution.

5. The ophthalmic solution according to claim 2 or 3 wherein the sodium flurbiprofen is present in an amount up to about 0.03% by weight per volume of the solution and the lauralkonium chloride is present in an amount up to about 0.005% by volume of the solution.

6. An ophthalmic solution comprising:

an acidic ophthalmologically acceptable drug formulation having a negative charge at physiological pH; and

a preservative consisting essentially of lauralkonium chloride and present in an antimicrobially effective amount.

7. The ophthalmic solution according to Claim 6 wherein said ophthalmologically acceptable drug formulation comprises sodium flurbiprofen.

8. The ophthalmic solution according to Claim 7 further comprising citric acid monohydrate, sodium citrate dihydrate, polyvinyl alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride, and water.

9. The ophthalmic solution according to Claims 6, 7 or 8 wherein said lauralkonium chloride is present in an amount up to about 0.005% by weight per volume of the solution.

10. The ophthalmic solution according to Claim 7 or 8 wherein the sodium flurbiprofen is present in an amount up to about 0.03% by weight per volume of the solution and the lauralkonium chloride is present in an amount up to about 0.005% by volume of the solution.

11. A method for preserving an acidic ophthalmically acceptable drug solution comprising adding to said ophthalmically acceptable drug solution an antimicrobially effective amount of lauralkonium chloride.

12. An ophthalmic solution comprising:

an acidic ophthalmologically acceptable drug capable of forming an insoluble ion-pair with benzalkonium chloride; and

a preservative consisting essentially of lauralkonium chloride and present in an antimicrobially effective amount.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 94/00188

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/19 A61K9/00 A61K47/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 112, no. 16, 16 April 1990, Columbus, Ohio, US; abstract no. 145590h, see abstract & JP,A,01 246 227 (SANTEN PHARMACEUTICAL CO.,LTD.) 2 October 1989 ---	1,3,4,6, 8,9,11, 12
A	DATABASE WPI Week 8231, Derwent Publications Ltd., London, GB; AN 82-64749E (31) see abstract & JP,A,57 102 817 (KAKENYAKU KAKO KK) 26 June 1982 -----	2,5,7,10

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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Information on patent family members

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